Comparison of the effects of propofol plus fentanyl with midazolam plus fentanyl on pr, qtc interval and qt dispersion in patients undergoing coronary artery surgery

Koroner arter cerrahisi planlanan hastalarda propofol-fentanil ile midazolam-fentanil'in pr, qtc aralığı ve qt dispersiyonu üzerindeki etkilerinin karşılaştırılması

Propofol and midazolam during cardiac surgery

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Öz

Amaç: Koroner arter bypass greftleme uygulanan hastalarda anestezi indüksiyonunda kullanılan propofol ve midazolamın myokardiyal homojenite markerları üzerindeki etkilerinin karşılaştırılması. Gereç ve Yöntem: Elektrokardiyografileri ve sol ventrikül sistolik fonksiyonları normal olan toplam 50 hasta anestezi indüksiyonu sırasında propofol (Grup 1, n=25, ortalama yaş: 68.28±10.44) veya midazolam (Grup 2, n=25, ortalama yaş: 67.88±8.90) verilmek üzere rastlantısal olarak iki gruba ayrıldı. İki grubun başlangıçta karşılaştırılabilir olduğunun tespiti için standart 12-derivasyonlu elektrokardiyografileri çekildi. Hastalar ameliyat öncesinde ve sonrasında ambulatuvar elektrokardiyogram ile monitörize edildi ve her hasta için tek tek ortalama QT süresi, QTc süresi, P dispersiyonu ve QT dispersiyonu hesaplandı. Bulgular: Temel karakteristik özelliklerin dağılımı iki grup arasında benzerdi. İki grup asrasında preoperatif değerlendirmede ortalama QT süresi, QTc süresi, QT dispersiyonu ve p-dalga dispersiyonu açısından anlamlı fark gözlenmedi. Postoperatif dönemde, iki grup arasında bireysel ortalama QT süresi, QTc süresi ve P dispersiyonu ortalamaları arasında anlamlı fark saptanmazken, bireysel ortalama QT dispersyonu ortalaması propofol grubunda midazolam grubuna kıyasla anlamlı düzeyde daha yüksekti (Grup 1 vs. Grup 2 için sırasıyla 32.80±13.07 vs. 24.60±9.34, p=0.01). Tartışma: Koroner arter bypass greftleme uygulanan hastalarda anestezi indüksiyonu sırasında midazolam myokardın elektriksel stabilitesi üzerine minimal bir etki oluştururken, propofol myokardiyal homojenliğin yeniden sağlanmasına bir miktar engel oluyor gibi görünmektedir.

Anahtar Kelimeler

Midazolam; Propofol; Kalp Cerrahisi; QT Dispersiyonu

Abstract

Aim: To compare the effects of propofol and midazolam on markers of myocardial homogeneity when used during anesthesia induction in patients undergoing coronary artery bypass grafting. Material and Method: A total of 50 patients with normal left ventricular systolic function and normal electrocardiogram were randomized into two groups as to receive propofol Group 1 (n=25, mean age: 68.28±10.44) or midazolam (n=25, mean age: 67.88±8.90) during induction of anesthesia. Standard 12-lead electrocardiograms were obtained just before induction of anesthesia to ensure baseline comparability of two groups. Patients were monitored with an ambulatory electrocardiogram before and after surgery, and individual average QT duration, QTc duration, P dispersion and QT dispersion were calculated. Results: Distribution of baseline characteristics were similar between two groups. Two groups were also similar regarding preoperative QT duration, QTc duration, QT dispersion and p-wave dispersion. Mean of individual average QT duration, QTc duration, and P dispersion did not differ significantly between two groups whereas mean of individual average QT dispersion was significantly higher in propofol group than that in midazolam group in the postoperative period (32.80±13.07 vs. 24.60±9.34, in Group 1 and 2, respectively, p=0.01). Discussion: Midazolam seems to have minimal effect on the electrical stability of the myocardium, whereas propofol is likely to limit recovery of myocardial homogeneity after CABG to some extent when used during induction of anesthesia.

Keywords

Midazolam; Propofol; Cardiac Surgery; QT Dispersion

DOI: 10.4328/JCAM.5161 Received: 17.06.2017 Accepted: 07.08.2017 Printed: 01.11.2017 J Clin Anal Med 2017;8(6): 461-5
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Introduction

It has long been known that anesthetic drugs cause depression of myocardial contractility by several mechanisms, including altered myocardial energy utilization and unbalanced mitochondrial ion exchange. These mechanisms were also suggested to be responsible for the pro-arrhythmogenic effects of some anesthetics such as volatile anesthetics [1, 2]. Volatile anesthetics, especially isoflurane and sevoflurane, were shown to prolong corrected QT duration and QT dispersion, both of which are known as electrocardiogram markers of torsadogenicity. Several other anesthetics including opioids, non-depolarizing neuromuscular blockers, and anticholinesterase-anticholinergic combinations may cause prolongation of QT duration and dispersion [3].

Arrhythmias, both atrial and ventricular of origin, are common especially during the early postoperative course after cardiac surgery [4-6]. Patients with extensive involvement of coronary arteries, especially those subjected to undergo multi-vessel coronary artery bypass graft (CABG) are particularly at risk for development of arrhythmias after surgery. This highlights the importance of choosing the less pro-arrhythmogenic anesthetics during anesthesia induction.

There have been several studies suggesting that propofol cause less QT and QTc prolongation when used in anesthesia induction before non-cardiac surgery [7-9] and this seems to be also true for midazolam [3]. However, it is unclear whether these could be translated into cardiac surgery setting. In the present study, we sought to compare the effects of midazolam and propofol on electrocardiogram markers of myocardial refractoriness, including QT, QTc, QT dispersion and p wave dispersion.

Material and Method

The study was approved by institutional ethics board of the Erzincan University (approval number:21142744-804.01-1060). All patients were informed about the study protocol and signed informed consent was obtained from each patient. This prospective randomized two arm study was conducted in anesthesiology department of an Erzincan University Hospital where cardiac surgery has routinely been performed between January 2015 and August 2015. The study was made up of patients aged between 30 to 80 years old, fulfilling American Society of Anesthesiologists physical status I- II who were scheduled to undergo elective isolated coronary artery bypass grafting with cardiopulmonary bypass support. Patients who were scheduled for off-pump surgery and/or those with a clear indication for combined valve surgery or ascending aorta replacement were not included. Patients who were receiving any anti-arrhythmic drug that may affect QTc interval and those with low ejection fraction (<45%) were excluded. An initial electrocardiogram was obtained, and it was assessed by an independent cardiologist. Patients who have atrial fibrillation, atrioventricular block of any degree, left or right bundle branch block, fascicular block of any type, extreme right or left axis deviation, left ventricular hypertrophy, loss of R wave progression on chest leads and those who had any other type of cardiac arrhythmias on initial electrocardiogram were excluded.

A standard 6-lead Holter electrocardiogram monitoring was begun 24 hours before surgery and monitoring was continued for 24hours after completion of the operation. Study data including baseline information and laboratory parameters were collected both before and after the operation. These consisted of age, gender, body weight, systolic blood pressure, diastolic blood pressure, creatinine kinase (CK), creatinine kinase myocardial band (CK-MB) and brain natriuretic peptide. All patients were premedicated with oral alprazolam 0.5 mg at the night before surgery, and the dose was repeated 2 hours before they arrive at the operating room. In the operating room, standard monitoring included invasive blood pressure monitoring via radial artery, eight lead electrocardiogram, and pulse oximetry. A central venous line was introduced through the right internal jugular vein. Anesthesia depth was monitored with bispectral index (BIS) and was kept between 40 and 50. In each patient, time of cardiopulmonary bypass, time of cross clamping and the total number of coronary target vessels were recorded.

Patients fulfilling above criteria were divided into two groups as to receive propofol Group 1 (n=25, mean age: 68.28±10.44) or midazolam (n=25, mean age: 67.88±8.90) during induction and maintenance of anesthesia. In propofol group, anesthesia was induced with 1.0 mg/kg of propofol and maintained with 0.1 mg/kg/min of propofol. In midazolam group, anesthesia was induced with 0.1 mg/kg of midazolam and maintained with 0.1 mg/kg/hour of midazolam. All patients received 5–10 microgram/kg of fentanyl and 1 mg/kg rocuronium were given before intubation. Fentanyl infusion was maintained at a rate of 3–5 microgram/kg/hour in both groups. QT, QTc, P dispersion and QT dispersion intervals were automatically calculated by the Holter ECG software, and the values were transferred into a computerized database by a blinded cardiologist. Average interval duration of a total of five measurements were calculated for each parameter in each patient. Discontinuation of the electrocardiogram monitoring was not required in any patient.

Statistical analysis

Statistical analyses were performed with SPSS (SPSS version 16.0 Inc. Chicago, IL. USA) software. Visual and analytical methods (Shapiro-Wilk's test) were used to test normal distribution. Continuous variables were defined as mean ± standard deviations. Parameters with normal distribution were compared using t-test whereas those with non-normal distribution were compared using Mann Whitney test. Paired samples t test was used to assess the difference between the preoperative and the postoperative measurement of QT, QTc, QTd and p dispersion. Categorical data were compared using chi-square test or Fisher's exact test. A p-value of less than 0.05 was considered to be statistically significant.

Results

Comparison of baseline characteristics of two groups was given in Table 1. Two groups were similar in terms of age (p=0.83), gender distribution (p=0.25), weight (p=0.46), systolic blood pressure (p=0.42) and diastolic blood pressure (p=0.13). Baseline laboratory parameters were similar between two groups, including mean CK (p=0.08), mean CK-MB (p=0.10) and mean BNP (p=0.38) levels. Two groups were comparable regarding mean QT duration (p=0.20), mean QTc duration (p=0.84), mean QT dispersion (p=0.47) and mean p wave dispersion (p=0.40) according to the 12-lead electrocardiograms taken before the operation.

Table 1. Baseline characteristics

Variable	Group 1 (Propofol group) (n=25)	Group 2 (Midazolam group) (n=25)	P value
Age	68.28±10.44	67.88±8.90	0.83
Male gender n (%)	14 (56.0%)	10 (40.0%)	0.25
Weight	74.88±12.65	77.16±11.63	0.46
Systolic blood pressure	139.56±21.73	135.40±16.44	0.42
Diastolic blood pressure	77.96±14.87	73.88±10.43	0.13
Creatinine kinase	127.12±173.09	64.72±42.73	0.08
Creatinine kinase myocardial band	21.80±18.84	15.46±8.43	0.10
Brain-type natriuretic peptide	223.20±385.931	138.52±211.87	0.38
Mean QT duration	378.60±42.11	395.20±43.50	0.20
Mean QTc duration	441.32±46.93	438.00±42.25	0.84
Mean QT dispersion	36.30±12.13	34.80±9.18	0.47
Mean P dispersion	27.40±11.91	24.40±10.03	0.40

There were no significant differences between two groups in regard to cross clamp time (47.40±10.71 vs. 45.68±5.63 in propofol vs. midazolam group, respectively, p=0.40), cardiopulmonary bypass time (92.00±5.80 vs. 91.20±4.58, in propofol vs. midazolam group, respectively, p=0.70), and number of coronary target vessels (3.84±0.90 vs. 4.12±0.83in propofol vs. midazolam group, respectively, p=0.25).

In both groups, means of individual average QTc duration, QTd, QT and P wave dispersion showed varying degrees of reduction after the operation. In group 1, the decreases in mean QTc (441.32±46.9 vs. 434.56±58.18, p=0.43), mean QTd (36.60±12.13 vs. 32.80±13.07, p=0.12) and mean p wave dispersion (27.40±11.91 vs. 24.60±13.06, p=0.05) were not of statistical significance whereas the decrease in mean QT was significant (378.60±42.11 vs. 365.40±46.09, p=0.03). In group 2, the decreases in mean QTc (438.00±42.25 vs. 410.80±54.99, p=0.014), mean QTd (34.80±9.18 vs. 24.60±9.34, p<0.001) and mean p wave dispersion (24.40±10.03 vs. 20.00±9.57, p=0.002) were of statistical significance whereas the decrease in mean QT was not significant (395.20±43.50 vs. 383.60±56.33, p=0.16).

Table 2 shows the comparison of study parameters in the postoperative period. Mean of individual average QT duration (365.40±46.09 vs. 383.60±56.33, in Group 1 and 2, respectively, p=0.40), QTc duration (434.56±58.18, 410.80±54.99,in Group 1 and 2, respectively, p=0.13) and P dispersion (24.60±13.06 vs. 20.00±9.57, in Group 1 and 2, respectively, p=0.26) did not differ significantly between two groups whereas individual average QT dispersion (32.80±13.07 vs. 24.60±9.34, in Group 1 and 2, respectively, p=0.01) was significantly higher in propofol group than that in midazolam group.

Table 2. Comparison of study parameters obtained in the postoperative period.

	Group 1 (Propofol group) (n=25)	Group 2 (Midazolam group) (n=25)	P value
QT	365.40±46.09	383.60±56.33	0.40
Corrected QT	434.56±58.18	410.80±54.99	0.13
P dispersion	24.60±13.06	20.00±9.57	0.26
QT dispersion	32.80±13.07	24.60±9.34	0.01
CK-MB	41.36±22.64	55.56±42.09	0.20
BNP	822.28±730	1265.80±852.54	0.09
Systolic blood pressure	99.44±32.63	123.92±17.89	0.008
Diastolic blood pressure	59.72±14.45	61.16±10.74	0.40

Discussion

Our study demonstrated that use of propofol is more likely to induce development of disparity in ventricular recovery compared to midazolam, as represented with higher QT dispersion, when used in anesthesia induction and maintenance in patients undergoing coronary artery bypass surgery. In addition, although anesthetic depth was maintained at similar levels in two groups, patients in propofol group had significantly lower systolic blood pressure levels at early stage after the operation. Taken together, propofol not only decreases cardiac output and inhibits contractility, but it also seems to have a negative effect on ventricular recovery after depolarization and thus it may cause prolongation of repolarization in patients undergoing cardiac surgery.

There have been several studies regarding the effect of anesthesia induction with propofol on QT or QTc prolongation whereas less is known about their effect on QT dispersion. In one study, Kleinsasser et al[10]. randomized a total of 30 females undergoing gynecologic surgery into two groups as to receive sevoflurane or propofol during anesthesia induction [10]. Inhaled induction with sevoflurane was found to be associated with a significant QTc prolongation whereas induction with propofol even shortened QTc. Sen et al]. compared the effects of sevoflurane inhalation with intravenous propofol on QTc interval during laparoscopic surgery [11]. The authors reported that rapid inhalation of 5% sevoflurane caused significant QTc prolongation whereas induction and maintenance of anesthesia with propofol did not cause any significant change in QTc duration. Similar results were obtained in children, as reported by Whyte et al. [12].

In contrast to these findings, an earlier study compared propofol with midazolam regarding their effect on QT prolongation in 30 patients without cardiovascular disease [13]. This study reported that both propofol and midazolam caused QT prolongation whereas no significant difference in post-induction QT intervals was found between patients receiving either medication. In line with these findings, we found no significant change in mean QT duration postoperatively in midazolam group and even a slight decrease was found in mean QT duration in propofol group. These findings should not be interpreted as ventricular recovery is not affected by induction and maintenance of anesthesia during coronary artery bypass surgery since QT duration itself does not act as the single indicator of the ventricular recovery.

Effect of propofol on QT dispersion has less commonly been addressed. In one study where a total of 29 patients with subarachnoid hemorrhage were included, it was reported that number of patients with increased QT dispersion was higher in the propofol group compared to thiopental group [14]. In controversy, Michaloudis et al. reported that propofol caused a decrease in both QT and QT dispersion in two cases with idiopathic prolonged QT interval and QT dispersion who underwent cardioverter-defibrillator device implantation [15]. In our

study, propofol was found to have no significant effect on QTc or QT dispersion whereas midazolam significantly reduced both QTc and QT dispersion after induction of anesthesia. Induction with propofol was associated with higher QT dispersion than midazolam in the postoperative period but this was mainly due to the substantial reduction in QT dispersion seen in midazolam group.

There is no doubt that presence of any underlying cardiac condition would confound the effect of anesthesia on myocardial recovery and homogeneity of cardiac repolarization. Ay et al. sought to determine whether QT dispersion was affected during intubation in patients with coronary artery disease [16]. It was reported that QT dispersion was found increased from 43.0±25.6 ms to 69.2±25.3 ($p<0.01$) ms in thiopental group and from 41.5±17.2 ms to 80.0±33.6 ms ($p<0.001$) in etomidate group. It was also reported that no change was seen in patients without coronary artery disease. As a controversy, in our study, QT dispersion was found reduced in both groups. These conflicting results may be due to several factors including study design, patient characteristics and extension of the coronary artery disease.

Effect of coronary revascularization on QTc and QT dispersion has also been addressed. Mirbolouk et al. hypothesized that enhancing the cardiac perfusion would improve ventricular homogeneity and electrical stability [17]. Their study included a total of 141 patients undergoing coronary revascularization (70 patients underwent percutaneous coronary intervention and 71 patients underwent CABG) and they obtained standard 12-lead electrocardiogram immediately before, immediately after, at 24th hour and at 7th day of surgery. The authors reported that QTc showed an early increase in postoperative period but decreased below preoperative levels at 7th day. In line with our results, the authors reported that there was a significant decrease in QT dispersion after the operation regardless of the type of procedure, indicating that revascularization seems to improve electrical stability of the myocardium.

In another study, study patients (n=44) were those undergoing simultaneous CABG and left ventricular aneurysmectomy. In this study, mean QT dispersion values were relatively higher both regarding the preoperative and postoperative period compared those we reported herein (65.29±29.25 and 51.76 ± 18.49 ms for preoperative and postoperative period, respectively). Although surgery seems to achieve a significant improvement in ventricular homogeneity, relatively higher QT dispersion in this study indicates the role of irreversible ventricular remodeling on disordered myocardial conduction [18]. Since our study excluded those patients with poor ventricular function, we could not draw a conclusion regarding the effect of coronary revascularization on myocardial homogeneity or electrical stability.

Our study had several limitations. Small sample size and single institution setting were the major limitations. Twenty-four-hour ambulatory electrocardiogram monitoring allowed us to obtain multiple measurements in each patient. This approach also ensured the leads stayed at the same place from beginning to the end of the study and provided information about any episode of arrhythmia. However, since all these measurements were based on 6-lead electrocardiogram tracings, our results should be cautiously interpreted especially if they are compared with results from previous studies where a standard 12-lead electrocardiogram was the accepted method.

In conclusion, CABG seems to reduce QT dispersion, however this effect might be affected by the type of anesthetic medication used for anesthesia induction. The reduction in QT dispersion was not statistically significant in propofol group whereas patients in the midazolam group had a significant decrease in mean QTd. Since midazolam is known to have a minimal effect on electrical stability of the myocardium, recovery of myocardial homogeneity after CABG might be limited to some extent by use of propofol during induction of anesthesia.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Onk D, Onk OA, Değirmenci H, Küçüksu Z, Bedir Z, Kuyrukluyıldız U, Ayazoğlu TA. Comparison of the Effects of Propofol Plus Fentanyl with Midazolam Plus Fentanyl on PR, QTC Interval and QT Dispersion in Patients Undergoing Coronary Artery Surgery. J Clin Anal Med 2017;8(6): 461-5.